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Summary
Members of the Developing Country Vaccine Regulators Network met together with members of the Paediatric Dengue Vaccine Initiative of the International Vaccine Institute, researchers, investigators and representatives of regulatory agencies from countries where PDVI works and there are trials running or planned in the future, to discuss the development of new dengue vaccines and the possible design of clinical trials that would support the introduction of such vaccines. Support was provided by expert members of the European Union and US regulatory affairs, and the WHO Access to Technology - Initiative for Vaccine Research division.

The background to the disease, epidemiology, and the past and current vaccine candidates were presented.

Discussions centred on the challenges encountered to date and the possible solutions. Future developments were described and ways to assist the Developing Countries in the promotion and regulation of clinical trials and eventual licensure of candidate vaccines were debated.

A number of issues were highlighted as of importance to the safe progress of this project.

Background
Dengue fever is caused by four arboviruses (flavivirus) - DEN 1-4, transmitted from infected humans by Aedes aegypti mosquitoes in tropical and subtropical urban and rural areas of the world.

There is no known animal reservoir of infection. It is primarily a febrile disease of disease of children - estimated 100 million cases per year, but may affect non-immune travellers to endemic areas. The reported number and the severity of cases are increasing.

There are four sero/genotypes and primary infection by any one type causes relatively mild, but unpleasant disease -Dengue fever-, and confers type-specific life-long immunity.

However, typically after subsequent infection by any one of the other types may lead to more severe disease syndrome of Dengue haemorrhagic fever or Dengue shock syndrome. These severe manifestations are estimated to affect 500 000 people per year and result in about 20 000 deaths. Management of the severe forms of Dengue disease is critical and survival rates in some areas are much higher due to good treatment practices. Cost of illness and strain to medical facilities are considerable.
Among other factors, the severe disease is believed to be associated with low levels of neutralizing antibody.

The prevalence of the different viral types in any one area is variable, with seasonal and annual changes that are reflected in the incidence of disease. The prevalence of several types in one region is common.

Thus a Dengue vaccine would need to confer full immunity to all four types simultaneously, and it is generally agreed that a tetravalent live attenuated vaccine would be the most effective option. A recombinant subunit vaccine design, is also in development and may yet prove of benefit.

Other successful Flavivirus vaccines are available, e.g. Yellow Fever and Japanese Encephalitis and the vaccines confer long immunity. Dengue infection confers life-long immunity against the infecting strain. Duration of immunity of these vaccines is currently unknown but may require regular boosting.

Development of a Dengue vaccine has been hampered by the complexity of the disease syndrome and fears that a sub-optimal vaccine could lead to additional enhanced-disease cases. There is no animal model of the disease that can be used to assist vaccine development or understanding of the disease mechanisms. Thus human clinical trials are the only mechanism to evaluate candidate vaccines for safety and efficacy.

A variety of candidate vaccines have been evaluated or are in development. Most experience has been gained from a live attenuated tetravalent, cell-culture vaccines derived from wild virus isolates. Other promising vaccines include deletion mutants, other types of chimeric constructs (Yellow Fever 17D + Dengue), subunit and DNA vaccines. Phase I and Phase II trials have been conducted in several regions world-wide with the live attenuated (chimeric and non-chimeric) vaccines. To date, no case of enhanced Dengue disease syndrome has been detected in any trial vaccinees.

Neutralizing antibody is currently the best candidate test for measuring a serological correlate of protection, but the lack of standardization of the Plaque Reduction Neutralisation Test (PRNT) has hampered establishment of clear cut serologic correlates of protection. There is indirect evidence of the importance of cell-mediated immunity.

Further research into diagnostic tests and methods of assessing immunity to disease is critical, and well designed clinical trials are essential to the development of an effective and affordable vaccine.
DCVRN Considerations and actions

1. The DCVRN Exco will nominate a representative member to attend the on-going WHO ECBS meetings tasked with the drafting of Dengue vaccine guidelines.

2. A further DCVRN meeting on Dengue vaccines is proposed for November 2007. This will include representatives of the existing vaccines in trials (GSK & Sanofi-Pasteur) as well as those developers with vaccines in earlier stages of development. (E.g. Butantan/ Brazil; Biological E and Panacea from India, Invirogen and Hawaii Biotech). In addition representatives of regulatory authorities in the vaccine-developer countries and other sponsors or promoters (PDVI) will be invited. Investigators of existing and planned clinical trials will also be encouraged to attend.

3. The DCVRN favours [should the development of formal procedures for collaboration and joint review of clinical trial applications and monitoring (GCP inspections) by the responsible National Regulatory authority, EMEA and/or FDA and concerned DCVRN members with facilitation by WHO. The cooperation/consensus of the Sponsor would be required.

4. Selection of suitable sites for clinical trials of Dengue vaccine candidates is important. Issues such as investigator experience, Dengue strain prevalence, NRA competence and the implications of rural vs urban sites, as well as multi-year longitudinal data on dengue incidence, and the ability to detect clinical dengue cases, should be considered during planning.

5. During monitoring of Dengue vaccine trials, the safety signals during the 1st year would be very important. In clinical trial design, improved definitions of AEFIs, are needed: e.g. vaccine induced AEFI / intercurrent infection / differentiation from infection induced severe disease. Improved safety surveillance and the importance of viral analysis early in all cases of fever is stressed.

6. The NRA in Dengue prevalent countries need to be open minded in considering new approaches to vaccine development but must ensure a favourable risk-benefit for the country. For example it may be necessary to consider an application for a clinical trial for a vaccine containing less than the four virus types prevalent in that country. NRA’s should also consider the proposal by the US FDA that proven efficacy against one strain in a tetravalent vaccine would be acceptable for registration - and
how this would influence the design of clinical trials and the requirements for post marketing surveillance. WHO clinical trial guidelines will provide additional guidance.

7. A common understanding of standard definitions is important. Standardized test methods and the acceptance of validated international reference standards for antibody responses and virus typing is needed. Clearer definition is needed for Phase II, Phase IIb and IIIb trials. The role of the WHO ECBS in providing these definitions is supported.

8. More human trials to establish the science of the severe disease syndrome, and the correlates of immunity would assist vaccine development. However, the ethical issues, should this require deliberately infecting subjects with a virus such as Dengue, would make such an approach unacceptable, taking into consideration the potential of enhancement of the disease. The development of an animal model for dengue disease syndromes would be of great benefit.

9. Future Phase III trials are planned, based on the safety and efficacy data from current Phase II trials in Thailand, Philippines and Mexico. It is important for the responsible NRAs to note that formulation or regimen changes need to be carefully evaluated in relation to the results from the prior clinical trials.

10. The formulation of the Investigational Product cannot be amended during the conduct of a phased series of clinical trials. A full review of quality, particularly related to vaccine stability and in-vial viral inactivation/interference, and safety is needed - perhaps including added Phase I studies.

11. PDVI will assist DCVRN members by identifying Independent experts to assess clinical trial applications. Other joint PDVI and DCVRN activities are encouraged, that may include other regulators and ensure that DCVRN concerns are taken into account. For example, PDVI is prepared to work with WHO/DCVRN on regulatory capacity building for dengue vaccine issues as well as ASEAN/Vaccine Chapter through the WHO link.
Summarized Presentations:

Bill Letson: PDVI & IVI, Korea.
**The disease: epidemiology and burden of disease of Dengue.**
A comprehensive overview of the disease burden, virus biology and transmission, diagnosis and current disease management practices.

Alan Barrett: Sealy Centre for Vaccine Development. University of Texas
**Current status of Dengue vaccine development**
The properties of the virus and the disease that make the development of a vaccine difficult are described. Candidate vaccines and concepts in development and in clinical trials are set out. The difficulties in defining the mechanism of protection from disease and the serological correlates of protection was discussed.

Joachim Hombach: WHO Initiative for Vaccine Research
**WHO Guidelines in relation to Dengue Vaccines**
This ongoing WHO Dengue Vaccine initiative has reached an advanced stage. The WHO has produced reports on serological correlates of protection and on the methods for assaying neutralizing antibody. The TRS 923 Guidelines for production and quality-control of candidate Dengue vaccines has been published, and further guidelines on the clinical evaluation of dengue vaccines are in preparation.

Harold Margolis: PDVI & IVI, Korea.
**Challenges for clinical evaluation of Dengue vaccines.**
The characteristics of an “ideal” dengue vaccine were contrasted with the likely reality. The issues that make the design of Dengue vaccine trials difficult, in particular the post-trial surveillance and other issues were outlined. The difficulties of defining efficacy end-points for vaccine trials was also high-lighted. The importance of post-marketing surveillance and risk management was noted.

Arunee Sabchareon: Mahidol University, Thailand
**Clinical trials of Dengue vaccines in Asia**
The conduct and outcomes of two clinical trials in Thailand and the Philippines were described. The tetravalent Mahidol-Aventis vaccine was found to be relatively reactogenic and further evaluation of the vaccine was discontinued. However, 7 years after the vaccine administration, it was shown to be immunogenic and no severe form of dengue disease [occurred] in the vaccine recipients exposed to wild type dengue infections was detected.[.]
Interim results of the tetravalent Chimerivax Dengue vaccine (Sanofi Pasteur – Acambis) showed satisfactory safety and low level of vaccine viral infectivity.

Harold Margolis: PDVI & IVI, Korea. (For Wellington Sun - CDC)

**Clinical trials of Dengue vaccines in the Americas.**
Dengue disease in the Americas differs from Asia - and is becoming increasingly endemic with sporadic epidemics. There is a need for a safe and effective vaccine. Strain variation by type and time is a challenge to conduct of clinical trials.

Robin Levis: Centre for Biologics Evaluation and Research, US-FDA

**Regulatory considerations for Dengue vaccine clinical trial development**
The requirements for clinical safety and efficacy for licensure in USA were described. The expectations for trial design and outcomes as well as post marketing activities were outlined.

Pieter Neels: FAHMP, Belgium & Member of the EU CHMP

**The EU Regulatory Experience: From clinical trial application to registration of a vaccine**
This was a general presentation with specific references to the problems of Dengue vaccines.

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**Reference Articles:**

WHO Task Force on Clinical trials of Dengue vaccine.
Draft report of Meeting. Atlanta GA, USA. 11 November 2006

ADT Barrett. Annals of the New York Academy of Sciences
Current status of Flavivirus vaccines

J Hombach et al. 2007. Vaccine, 25; 4130-4139
Scientific consultation on immunological correlates of protection induced by dengue vaccines